

REMARKS

Favorable consideration and allowance are respectfully requested for claims 1 and 3-67 in view of the following remarks.

The Examiner is thanked for the careful review and consideration of this case and the withdrawal of the rejection of claims 11 and 12 under 35 U.S.C. § 112, second paragraph, is acknowledged with appreciation.

35 U.S.C. § 112, first paragraph

The rejection of claims 1 and 3-67 as allegedly lacking enablement is respectfully traversed.

The standard for adequate enablement is whether the specification describes the claimed subject matter in such a way as to enable a person skilled in the art to which it pertains to use the invention. Thus, enablement is judged in view of the combined teachings of the specification and the knowledge of one skilled in the art.

The rejection is predicated on the fact that the invention claims a broad range of salts of salt-forming pharmaceutically active agents. Applicants note that the concept of salt-formation is not unpredictable. On the contrary, it is well known that pharmaceutically active agents with basic groups, such as amino functions, will form salts with acids. Moreover, it is not unpredictable that salts of pharmaceutically active agents with different anions will have different solubilities. This is true over the broad range of pharmaceutically active agents and does not in any way vary or depend upon the particular pharmaceutical activity of the agent.

Furthermore, the description provides explicit guidance for:

- Salt formation (page 3, lines 12-17);
- A list of compounds for salt formation with the active substance (page 5, line 28 to page 6, line 5 and page 6, lines 18-23)

- A method for determining the water solubility of a salt of an active substance (page 17, lines 13-31);
- A method for preparing a dosage form of the active ingredient salts (page 14, line 28 to page 15, line 26);
- A method for applying a protective coating in cases where the acidic component of the salt is a weaker acid than the hydrochloric acid in the stomach (page 10, line 32 to page 11, line 32); and
- A process for applying coatings (page 12, lines 9-29 and page 15, line 28 to page 16, line 19).

Inasmuch as none of these aspects of the claimed invention is unpredictable, applicants submit that a person of ordinary skill in the art guided by the teachings of the specification would be able to make and use the claimed invention as broadly as claimed.

Pointedly, the Office Action does not explain why a person skilled in the art would be unable to make or use salts of any of the pharmaceutically active ingredients embraced by the claim, nor does the Office Action give any example of a pharmaceutically active agent embraced by the claim with which a person of ordinary skill in the art would be unable to practice the invention. Again, applicants point out that because the phenomenon of the invention does not depend on the particular pharmaceutical activity of the active ingredient, the fact that the claim embraces agents with a broad variety of pharmaceutical activities is irrelevant. Salt formation is not unpredictable, and the teachings and examples of the specification are sufficient to demonstrate the effectiveness of the claimed invention over the entire range of claimed salt-forming pharmaceutically active agents.

The U.S. Court of Customs and Patent Appeals has stated that "The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA

1971). The court also added that “it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.” *In re Marzocchi*, 169 USPQ 367 , 370 (CCPA 1971). The present record includes no statement or other explanation as to why the truth of the accuracy of statements in the disclosure should be doubted. The law does not require a separate showing of functionality for each and every drug encompassed by a claim.

The Office Action’s assertion that “the bioavailability of a particular salt, in particular in conjunction with another salt of the same active agent . . . cannot be known.” This conclusion is made without any evidence to support it. The only evidence in the present record relating to the claimed mixtures of salts of a particular active agent is that submitted by the Applicant. The conclusion that the bioavailability of a particular salt cannot be known or that the bioavailability effects of combining multiple salts of the same agent is unfounded and unsupported by the present record. Moreover, Applicants reiterate that because the phenomenon of the invention does not depend on the particular pharmaceutical activity of the active ingredient, the fact that the claim embraces agents with a broad variety of pharmaceutical activities is irrelevant.

In the absence of any explanation of a reason why a person of ordinary skill in the pharmaceutical art would not be able to make and use salt mixtures as claimed, the statements in the disclosure must be considered enabling, and the rejection cannot stand.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

35 U.S.C. § 103

The rejection of claims 1-9, 11, 12, 15, 17, 18, 21, 30-32, 55-58 and 62-67 as obvious over Oshlack et al., WO 99/01111, in view of Sackler, U.S. 5,478,577, is also respectfully traversed. Oshlack et al. disclose sustained release oral solid dosage forms of various pharmaceutically active agents, including salts. Applicants agree with the statement in the Office Action that Oshlack et al. does not disclose explicitly disclose the use of mixtures of salts of tramadol. In fact, the reference fails to disclose or suggest in any way using a mixture of two different salts of the same pharmaceutically active ingredient having different solubilities as is presently claimed.

Sackler fails to make up for the deficiencies of Oshlack to teach mixtures of salts of the same pharmaceutically active ingredient. Sackler is directed to “sustained release opioid formulations which upon administration quickly release an effective portion of the opioid.” As such, a person of skill in the art would generally understand the reference to teach using the same active substance (or mixtures of different active ingredients) in an unretarded (immediate release) and retarded delivery form.

The Office Action cites the paragraph bridging columns 6 and 7 as teaching using mixtures of salts of tramadol. This reading of that paragraph is not commensurate with the understanding a person of skill in the art would gain from the language in that paragraph. The paragraph recites a number of opioid analgesics and then lists salts thereof and mixtures of any of the foregoing. A person of skill in the art would understand the mixtures to refer to mixtures of different pharmaceutically active ingredients. There is nothing to suggest to a person of skill in the art to use or even try to use mixtures of different salts of the same pharmaceutically active ingredients.

Situations involving mixtures of two different pharmaceutically active agents are very different from mixtures of two different salts of the same active agent as claimed in the present invention. The record is devoid of any example

of a mixture of different salts of the same active agent, and with good reason. A person of skill in the art would have no reason to expect that a mixture of two different salts of the same active ingredient would provide any benefit beyond either of the salts alone. There is nothing in the present record which would lead a person of skill in the art to expect any advantage from using a mixture of two materials over using a single material when there is only one active ingredient present in the mixture. The formation of a mixture of two different salts of the same active ingredient is unquestionably more troublesome and inconvenient than the provision of a single salt.

All that the prior art would lead a person of ordinary skill in the art to expect would be that such a mixture of salts of the same active ingredient would have the same effect as a single salt of the active ingredient. Thus, the prior art gives a person of ordinary skill in the art no reason or motivation to form such a mixture of salts of the same active ingredient. Accordingly, it cannot be fairly be said to be obvious for a person of ordinary skill to incur the trouble and inconvenience of forming such a mixture for no reason.

Not only does the cited art fail to teach or suggest the use of a mixture of different salts of the same active ingredient, the present record provides no teaching or other suggestion to use a mixture of salts having solubilities which differ from one another by at least a factor of two.

The Office Action acknowledges receipt of the declaration filed May 25, 2004, however the remarks do not provide any reference to the declaration and the Office Action does not appear to reflect consideration of the results shown therein.

The Declaration of Dr. Bartholomaeus shows test results comparing the release profile of: (i) tramadol hydrochloride, (ii) tramadol saccharinate and (iii) a mixture of tramadol hydrochloride and tramadol saccharinate. The results show that the drug release profile may be adjusted by having different salts of the same active substance in a single formulation.

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Only the present applicants have recognized that unexpected advantages could be attained from using a mixture of at least two different salts of the same active ingredient having different solubilities as is presently claimed. Consequently, it is only after a consideration of the applicant's disclosure that there is any reason or motivation to try to form such a mixture. Such hindsight analysis is clearly improper.

Under the facts of this case, the state of the art fails to teach or suggest a combination of at least two different salts of the same active ingredient having different solubilities as claimed. Further, the record provides no showing of anything that would motivate one of skill in the art to try to modify the disclosures of the cited references so as to arrive at the claimed invention. Accordingly, a *prima facie* showing of obviousness has not been made. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

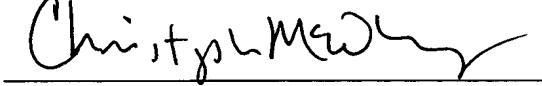
If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

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Although a petition for an Extension of Time is submitted herewith, if necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029310.50986US).

Respectfully submitted,

January 4, 2006



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